AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of claims:

1. (Withdrawn) A composition comprising an opioid narcotic analgesic and a nontoxic VR1 antagonist.

2. (Withdrawn) The composition of claim 1 wherein the narcotic analgesic is selected from alfentanyl, alphaprodine, anileridine, bezitramide, codeine, dihydrocodeine, diphenoxylate, ethylmorphine, fentanyl, heroin, hydrocodone, hydromorphone, isomethadone, levomethorphan, levorphanol, meperidine, metazocine, methadone, metopon, morphine, opium, oxycodone, oxymorphone, pethidine, phenazocine, piminodine, racemethorphan, racemorphan, thebaine, their mixtures and their pharmaceutically acceptable salts and hydrates.

3. (Withdrawn) The composition of claim 1, wherein the narcotic analgesic is selected from codeine, fentanyl, hydrocodone, meperidine, morphine, oxycodone, their mixtures and their pharmaceutically acceptable salts and hydrates.

4. (Withdrawn) The composition of claim 1, wherein the VR1 antagonist is not a vanilloid compound.

5. (Withdrawn) The composition of claim 1, wherein the VR1 antagonist exhibits a K_i value of 1 micromolar or less in a capsaicin receptor binding assay.

6. (Withdrawn) The composition of claim 1, wherein the VR1 antagonist exhibits a K_i value of 100 nanomolar or less in a capsaicin receptor binding assay.

7. – 24. (Cancelled)

25. (Withdrawn) A packaged pharmaceutical composition, comprising:

(i) a nontoxic VR1 antagonist;

(ii) an opioid narcotic analgesic; and

(iii) instructions indicating that the VR1 antagonist and opioid narcotic analgesic are to be administered to a patient for the treatment of pain.

26. (Withdrawn) The packaged pharmaceutical composition of claim 25, wherein the VR1 antagonist and narcotic analgesic are present in the same composition.

27. (Withdrawn) The packaged pharmaceutical composition of claim 25, wherein the VR1 antagonist and narcotic analgesic are present in different containers.

28. (Withdrawn) The packaged pharmaceutical composition of claim 25, wherein the VR1 antagonist and narcotic analgesic are formulated for oral administration.

29. (Withdrawn) The packaged pharmaceutical composition of claim 25, wherein the VR1 antagonist is not a vanilloid compound.

30. (Withdrawn) The packaged pharmaceutical composition of claim 25, wherein the VR1 antagonist exhibits a K_i of 1 micromolar or less in a capsaicin receptor binding assay.

31. (Withdrawn) The packaged pharmaceutical composition of claim 25, wherein the VR1 antagonist exhibits a K_i of 100 nanomolar or less in a capsaicin receptor binding assay.

32. (Withdrawn) The packaged pharmaceutical composition of claim 25, wherein the VR1 antagonist is present in a tolerance-reducing amount.

33. (Withdrawn) The packaged pharmaceutical composition of claim 25, wherein the VR1 antagonist is present in a dependence-reducing amount.

34. (Withdrawn) The packaged pharmaceutical composition of claim 25, wherein the VR1 antagonist is present in a pain relief-enhancing amount.

35. (Withdrawn) The composition of claim 26 wherein the narcotic analgesic is selected from alfentanyl, alphaprodine, anileridine, bezitramide, codeine,

dihydrocodeine, diphenoxylate, ethylmor6hine, fentanyl, heroin, hydrocodone, hydromorphone, isomethadone, levomethorphan, levorphanol, meperidine, metazocine, methadone, metopon, morphine, opium, oxycodone, oxymorphone, pethidine, phenazocine, piminodine, racemethorphan, racemorphan, thebaine, their mixtures and their pharmaceutically acceptable salts and hydrates.

36. (Withdrawn) The packaged pharmaceutical composition of claim 35, wherein the narcotic analgesic is selected from codeine, fentanyl, hydrocodone, meperidine, morphine, oxycodone, their mixtures and their pharmaceutically acceptable salts and hydrates.

37. (Withdrawn) The packaged pharmaceutical composition of claim 25 in sustained release dosage form.

38. (Withdrawn) A method of treating pain in a patient, comprising administering to a patient, simultaneously or sequentially in either order;

(i) an opioid narcotic analgesic; and

(ii) a nontoxic VR1 antagonist;

and thereby providing pain relief to the patient.

39. (Withdrawn) The method of claim 38, wherein the narcotic analgesic is selected from alfentanyl, alphaprodine, anileridine, bezitramide, codeine, dihydrocodeine, diphenoxylate, ethylmorphine, fentanyl, heroin, hydrocodone, hydromorphone, isomethadone, levomethorphan, levorphanol, metazocine, methadone, metopon, meperidine, morphine, opium, oxycodone, oxymorphone, pethidine, phenazocine, piminodine, racemethorphan, racemorphan, thebaine, their mixtures and their pharmaceutically acceptable salts and hydrates.

40. (Withdrawn) The method of claim 38, wherein the VR1 antagonist is not a vanilloid compound.

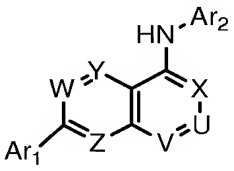
41. (Withdrawn) The method of claim 38, wherein the VR1 antagonist exhibits a K_i value of 1 micromolar or less in a capsaicin receptor binding assay

42. (Withdrawn) The method of claim 38, wherein the VR1 antagonist exhibits a K_i value of 100 nanomolar or less in a capsaicin receptor binding assay.

43. (Currently amended) A method for inhibiting the development of tolerance to an opioid narcotic analgesic in a patient, comprising continuously or repeatedly administering to a patient, simultaneously or sequentially in either order;

(i) an opioid narcotic analgesic; and

(ii) a tolerance-reducing amount of a nontoxic VR1 antagonist represented by the formula (Formula II):



Formula II

or a pharmaceutically acceptable salt thereof, wherein

V and X are each independently N or CR_1, with the proviso that at least one of V and X is N; U is N or CR_2, with the proviso that if V and X are N, then U is CR_2; and W, Y and Z are each independently N or CR_1;

R_1 is independently selected at each occurrence from hydrogen, halogen, hydroxy, cyano, amino, C_1-C_8alkyl, haloC_1-C_8alkyl, C_1-C_8alkoxy, haloC_1-C_8alkoxy and mono- and di-(C_1-C_8alkyl)amino~~. Within certain embodiments, each R_1 is independently hydrogen, C_1-C_4alkyl or haloC_1-C_4alkyl; in other embodiments, each R_1 is H~~;

R_2 is:

(i) hydrogen, halogen, cyano or -COOH;

(ii) C_2-C_8alkoxycarbonyl, C_1-C_8alkanoyl, C_2-C_8alkanone, C_1-C_8alkanoyloxy, C_1-C_8carbonate or C_1-C_8carbamate, each of which is unsubstituted or substituted with from 1 to 9 substituents independently selected from R_b or R_d; or

(iii) a group of the formula $-R_c$-M-A-R_y, wherein: R_c is C_0-C_3alkyl; M is a bond, N(R_z), O, S, SO_2, -C(=O)$_p$N(R_z), N(R_z)C(=O)$_p$, SO_2N(R_z), or N(R_z)SO_2, wherein

p is 0 or 1;

A is a bond or C_1-C_8alkyl optionally substituted with from 1 to 3 substituents independently chosen from R_b or R_d; and

R_y and R_z are independently

(a) hydrogen, C_1-C_8alkyl, C_2-C_8alkanone, C_2-C_8alkyl ether, C_2-C_8alkenyl, a 4- to 10-membered carbocycle or heterocycle, or

(b) joined to R_c to form a 4- to 10-membered carbocycle or heterocycle, wherein each R_y and R_z is independently unsubstituted or substituted with from 1 to 9 substituents independently selected from R_b or R_d; or R_y and R_z are joined to form a 4- to 10-membered heterocycle that is unsubstituted or substituted with from 1 to 9 substituents independently selected from R_b or R_d;

R_b is independently chosen at each occurrence from hydroxy, halogen, amino, aminocarbonyl, amido, cyano, nitro, oxo, C_1-C_8alkyl, C_1-C_8alkoxy, C_1-C_8alkylthio, C_1-C_8alkyl ether, hydroxyC_1-C_8alkyl, haloC_1-C_8alkyl, phenyl, phenyl(C_1-C_8alkyl), mono-and di-(C_1-C_6alkyl)amino, (SO_2)C_1-C_8alkyl, 5- to 7-membered heterocycle and (5- to 7-membered heterocycle)(C_1-C_8alkyl);

R_d is independently selected at each occurrence from hydroxy, halogen, amino, aminocarbonyl, amido, cyano, nitro, C_1-C_8alkyl, C_1-C_8alkylthio, hydroxyC_1-C_8alkyl, haloC_1-C_8alkyl, phenyl, phenyl(C_1-C_8alkyl), mono-and di-(C_1-C_6alkyl)amino, (SO_2)C_1-C_8alkyl, 5- to 7-membered heterocycle and (5- to 7-membered heterocycle)(C_1-C_8alkyl);

Ar_1 and Ar_2 are independently selected from 5- to 10-membered aromatic carbocycles and heterocycles, each of which is unsubstituted or substituted with from 1 to 3 substituents independently selected from groups of the formula LR_a;

L is independently selected at each occurrence from a bond, -O-, -C(=O)-, -OC(=O)-, -C(=O)O-, -O-C(=O)O-, -$S(O)_m$-, -NR_x-, -C(=O)NHR_x-, -NHR_xC(=O)-, -$NR_xS(O)_m$-, -$S(O)_mNR_x$- and –$N[S(O)_mR_x]S(O)_m$-;

wherein

m is independently selected at each occurrence from 0, 1 and 2; and R_x is independently selected at each occurrence from hydrogen and C_1-C_8alkyl;

R_a is independently selected at each occurrence from: (i) hydrogen, halogen, cyano and nitro; and (ii) C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkynyl, C_2-C_8alkyl ether, 3- to 10-membered heterocycles, mono- and di-(C_1-C_8alkyl)amino and (3- to 10-membered heterocycle)C_1-C_6alkyl, each of which is optionally substituted with from 1 to 9 substituents independently selected from R_b;

and thereby inhibiting the development of tolerance to the opioid narcotic analgesic.

44. (Previously presented) The method of claim 43, wherein the opioid narcotic analgesic is selected from alfentanyl, alphaprodine, anileridine, bezitramide, codeine, dihydrocodeine, diphenoxylate, ethylmorphine, fentanyl, heroin, hydrocodone, hydromorphone, isomethadone, levomethorphan, levorphanol, meperidine, metazocine, methadone, metopon, morphine, opium, oxycodone, oxymorphone, pethidine, phenazocine, piminodine, racemethorphan, racemorphan, thebaine, their mixtures and their pharmaceutically acceptable salts and hydrates.

45. (Original) The method of claim 43, wherein the VR1 antagonist is not a vanilloid compound.

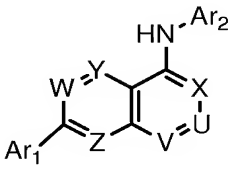
46. (Previously presented) The method of claim 43, wherein the VR1 antagonist exhibits a K_i value of 1 micromolar or less in a capsaicin receptor binding assay.

47. (Original) The method of claim 43, wherein the VR1 antagonist exhibits a K_i value of 100 nanomolar or less in a capsaicin receptor binding assay.

48. (Currently amended) A method for inhibiting the development of dependence on an opioid narcotic analgesic in a patient, comprising continuously or repeatedly administering to a patient, simultaneously or sequentially in either order;

(i) an opioid narcotic analgesic; and

(ii) a dependence-reducing amount of a nontoxic VR1 antagonist represented by the formula (Formula II):



Formula II

or a pharmaceutically acceptable salt thereof, wherein

V and X are each independently N or CR_1, with the proviso that at least one of V and X is N; U is N or CR_2, with the proviso that if V and X are N, then U is CR_2; and W, Y and Z are each independently N or CR_1;

R_1 is independently selected at each occurrence from hydrogen, halogen, hydroxy, cyano, amino, C_1-C_8alkyl, haloC_1-C_8alkyl, C_1-C_8alkoxy, haloC_1-C_8alkoxy and mono- and di-(C_1-C_8alkyl)amino~~. Within certain embodiments, each R_1 is independently hydrogen, C_1-C_4alkyl or haloC_1-C_4alkyl; in other embodiments, each R_1 is H~~;

R_2 is:

(i) hydrogen, halogen, cyano or -COOH;

(ii) C_2-C_8alkoxycarbonyl, C_1-C_8alkanoyl, C_2-C_8alkanone, C_1-C_8alkanoyloxy, C_1-C_8carbonate or C_1-C_8carbamate, each of which is unsubstituted or substituted with from 1 to 9 substituents independently selected from R_b or R_d; or

(iii) a group of the formula $–R_c$-M-A-R_y, wherein: R_c is C_0-C_3alkyl; M is a bond, N(R_z), O, S, SO_2, -C(=O)$_p$N(R_z), N(R_z)C(=O)$_p$, SO_2N(R_z), or N(R_z)SO_2, wherein

p is 0 or 1;

A is a bond or C_1-C_8alkyl optionally substituted with from 1 to 3 substituents independently chosen from R_b or R_d; and

R_y and R_z are independently

(a) hydrogen, C_1-C_8alkyl, C_2-C_8alkanone, C_2-C_8alkyl ether, C_2-C_8alkenyl, a 4- to 10-membered carbocycle or heterocycle, or

(b) joined to R_c to form a 4- to 10-membered carbocycle or heterocycle, wherein each R_y and R_z is independently unsubstituted or substituted with from 1 to 9 substituents independently selected from R_b or R_d; or R_y and R_z are joined to

form a 4- to 10-membered heterocycle that is unsubstituted or substituted with from 1 to 9 substituents independently selected from R_b or R_d;

R_b is independently chosen at each occurrence from hydroxy, halogen, amino, aminocarbonyl, amido, cyano, nitro, oxo, C_1-C_8alkyl, C_1-C_8alkoxy, C_1-C_8alkylthio, C_1-C_8alkyl ether, hydroxyC_1-C_8alkyl, haloC_1-C_8alkyl, phenyl, phenyl(C_1-C_8alkyl), mono-and di-(C_1-C_6alkyl)amino, (SO_2)C_1-C_8alkyl, 5- to 7-membered heterocycle and (5- to 7-membered heterocycle)(C_1-C_8alkyl);

R_d is independently selected at each occurrence from hydroxy, halogen, amino, aminocarbonyl, amido, cyano, nitro, C_1-C_8alkyl, C_1-C_8alkylthio, hydroxyC_1-C_8alkyl, haloC_1-C_8alkyl, phenyl, phenyl(C_1-C_8alkyl), mono-and di-(C_1-C_6alkyl)amino, (SO_2)C_1-C_8alkyl, 5- to 7-membered heterocycle and (5- to 7-membered heterocycle)(C_1-C_8alkyl);

Ar_1 and Ar_2 are independently selected from 5- to 10-membered aromatic carbocycles and heterocycles, each of which is unsubstituted or substituted with from 1 to 3 substituents independently selected from groups of the formula LR_a;

L is independently selected at each occurrence from a bond, -O-, -C(=O)-, -OC(=O)-, -C(=O)O-, -O-C(=O)O-, -S(O)$_m$-, -NR$_x$-, -C(=O)NHR$_x$-, -NHR$_x$C(=O)-, -NR$_x$S(O)$_m$-, -S(O)$_m$NR$_x$- and –N[S(O)$_m$R$_x$]S(O)$_m$-;

wherein

m is independently selected at each occurrence from 0, 1 and 2;

and R_x is independently selected at each occurrence from hydrogen and C_1-C_8alkyl;

R_a is independently selected at each occurrence from: (i) hydrogen, halogen, cyano and nitro; and (ii) C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkynyl, C_2-C_8alkyl ether, 3- to 10-membered heterocycles, mono- and di-(C_1-C_8alkyl)amino and (3- to 10-membered heterocycle)C_1-C_6alkyl, each of which is optionally substituted with from 1 to 9 substituents independently selected from R_b;

and thereby inhibiting the development of dependence on the opioid narcotic analgesic.

49. (Previously presented) The method of claim 48, wherein the opioid narcotic analgesic is selected from alfentanyl, alphaprodine, anileridine, bezitramide,

codeine, dihydrocodeine, diphenoxylate, ethylmorphine, fentanyl, heroin, hydrocodone, hydromorphone, isomethadone, levomethorphan, levorphanol, meperidine, metazocine, methadone, metopon, morphine, opium, oxycodone, oxymorphone, pethidine, phenazocine, piminodine, racemethorphan, racemorphan, thebaine, their mixtures and their pharmaceutically acceptable salts and hydrates.

50. (Original) The method of claim 48, wherein the VR1 antagonist is not a vanilloid compound.

51. (Original) The method of claim 48, wherein the VR1 antagonist exhibits a K_i value of 1 micromolar or less in a capsaicin receptor binding assay.

52. (Original) The method of claim 48, wherein the VR1 antagonist exhibits a K_i value of 100 nanomolar or less in a capsaicin receptor binding assay.

53. (Withdrawn) A method for enhancing narcotic analgesic-induced pain relief in a patient, comprising administering to a patient, simultaneously or sequentially in either order;

(i) an opioid narcotic analgesic; and

(ii) a pain-relief enhancing amount of a nontoxic VR1 antagonist;

and thereby enhancing narcotic analgesic-induced pain relief in the patient.

54. (Withdrawn) The method of claim 53, wherein the opioid narcotic analgesic is selected from alfentanyl, alphaprodine, anileridine, bezitramide, codeine, dihydrocodeine, diphenoxylate, ethylmorphine, fentanyl, heroin, hydrocodone, hydromorphone, isomethadone, levomethorphan, levorphanol, meperidine, metazocine, methadone, metopon, morphine, opium, oxycodone, oxymorphone, pethidine, phenazocine, piminodine, racemethorphan, racemorphan, thebaine, their mixtures and their pharmaceutically acceptable salts and hydrates.

55. (Withdrawn) The method of claim 53, wherein the VR1 antagonist is not a vanilloid compound.

56. (Withdrawn) The method of claim 53, wherein the VR1 antagonist exhibits a K_i value of 1 micromolar or less in a capsaicin receptor binding assay.

57. (Withdrawn) The method of claim 53, wherein the VR1 antagonist exhibits a K_i value of 100 nanomolar or less in a capsaicin receptor binding assay.

58. (Cancelled)

59. (Withdrawn) A single dose pharmaceutical composition for the treatment of a patient experiencing pain comprising a combination of a VR1 antagonist and at least one analgesic selected from the group consisting of less than about 25 mg of anileridine, less than about 25 mg of codeine, less than about 40 mg of dextropropositphene, less than about 25 mg of dihydrocodeine, less than about 4 mg of diphenoxylate, less than about 20μg of fenantyl, less than about 2 mg of hydrocodone, less than about 1.5 mg of hydromorphone, less than about 0.8 mg of levorphanol, less than about 20 mg of meperidine, less than abut 4 mg of methadone, less than about 7.5 mg of morphine, less than about 2 mg of oxycodon, less than about 0.8 mg of oxymorphone, less than about 0.8 mg of oxymorphone, less than about 40 mg of pethidine.

60. (Previously presented) The method of claim 43, wherein the VR1 antagonist is non-peptide.

61. (Previously presented) The method of claim 48, wherein the VR1 antagonist is non-peptide.

62. (Previously presented) The method of claim 43, wherein the VR1 antagonist is multi-aryl.

63. (Previously presented) The method of claim 48, wherein the VR1 antagonist is multi-aryl.

64. (Previously presented) The method of claim 43, wherein the opioid narcotic analgesic is administered at less than ¾ of the maximum dose advised by the manufacturer of the narcotic analgesic.

65. (Previously presented) The method of claim 43, wherein the opioid narcotic analgesic is administered at less than ½ of the maximum dose advised by the manufacturer of the narcotic analgesic.

66. (Previously presented) The method of claim 43, wherein the opioid narcotic analgesic is administered at less than ¼ of the maximum dose advised by the manufacturer of the narcotic analgesic.

67. (Previously presented) The method of claim 43, wherein the opioid narcotic analgesic is administered at less than 10% of the maximum dose advised by the manufacturer of the narcotic analgesic.

68. (Previously presented) The method of claim 48, wherein the opioid narcotic analgesic is administered at less than ¾ of the maximum dose advised by the manufacturer of the narcotic analgesic.

69. (Previously presented) The method of claim 48, wherein the opioid narcotic analgesic is administered at less than ½ of the maximum dose advised by the manufacturer of the narcotic analgesic.

70. (Previously presented) The method of claim 48, wherein the opioid narcotic analgesic is administered at less than ¼ of the maximum dose advised by the manufacturer of the narcotic analgesic.

71. (Previously presented) The method of claim 48, wherein the opioid narcotic analgesic is administered at less than 10% of the maximum dose advised by the manufacturer of the narcotic analgesic.